

***REMARKS/ARGUMENTS******The Invention***

The invention pertains to a method for slowing the progression of a tumor due to a genetic defect in the p53 gene, a method for delaying the onset of tumor formation or slowing the progression of a tumor due to ataxia telangiectasia or Li Fraumeni syndrome, and a method for delaying the onset of tumor formation.

***The Pending Claims***

Claims 1, 4-7, 9-20, 28, 30-34, 36-47, and 49 are currently pending. Claims 1, 4-7, and 9-20 are directed to a method for slowing the progression of a tumor due to a genetic defect in the p53 gene. Claim 28 is directed to a method for delaying the onset of tumor formation or slowing the progression of a tumor due to ataxia telangiectasia or Li Fraumeni syndrome. Claims 30-34, 36-47, and 49 are directed to a method for delaying the onset of tumor formation. Claims 4-7, 9-20, 31-34, and 36-47 have been withdrawn from consideration by the Office as being directed to a non-elected species. Applicants understand that, upon the allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141.

***The Amendments to the Claims***

Claims 1, 28, and 30 have been amended to recite "delaying the onset of tumor formation" and/or "slowing the progression of a tumor" and claim 49 has been amended to recite "tumor" as supported by the specification at, for example, page 10, lines 27-30. The claims also have been amended to narrow the breadth of the claims, without disclaimer or estoppel, as supported by the specification at, for example, page 7, line 24, through page 10, line 14. Claims 8, 21, 35, and 48 have been canceled. Formula II has been deleted from the claims as being directed to a non-elected invention, and claims 1, 28, and 30 have been amended to recite "compound of Formula I," as supported by the specification. No new matter has been added by way of this amendment.

*Examiner Interview*

Applicants thank Examiner Kwon for the courtesy of the telephonic interview of July 14, 2005, with one of Applicants' representatives, Heather Kissling, during which the enablement rejection was discussed. During the interview, Examiner Kwon proposed claim language, especially the preamble, which Applicants have adopted by way of the amendments presented herein. As such, the claim amendments could not have been previously presented.

*Summary of the Office Action*

The Office has maintained the rejection of claims 1, 28, 30, and 49 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Claims 30 and 49 remain rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claim 22 of U.S. Patent No 5,462,946 (hereinafter "the '946 patent") and/or claim 2 of U.S. Patent No. 6,605,619 (hereinafter "the '619 patent"). Reconsideration of the rejections is hereby requested.

*Discussion of Rejection under 35 U.S.C. § 112, first paragraph*

Claims 1, 28, 30, and 49 are rejected for alleged lack of enablement. The Office contends that the specification does not enable a method for the therapeutic or prophylactic treatment of all cancers or all cancers due to a defect in a p53 gene or due to ataxia telangiectasia or Li Fraumeni syndrome. Applicants note that the claims are not directed to a method of treating ataxia telangiectasia or Li Fraumeni syndrome, as asserted by the Office at page 4, last paragraph, of the Office Action, but tumors caused by ataxia telangiectasia or Li Fraumeni syndrome. The enablement rejection is traversed for the reasons set forth below.

The nature of the invention has been further sharpened by the claim amendments. The claims have been amended to replace the language directed to prophylactic treatment of cancer with "delaying the onset of tumor formation," as suggested by the Examiner during the telephonic interview of July 14<sup>th</sup>. The original claim language directed to therapeutic treatment of cancer has been replaced with "slowing the progression of a tumor." In addition, the claims have been amended to narrow the breadth of the claims. Contrary to the assertion of the Office at pages 4-5 of the Office Action, the amended claims do not require complete elimination or complete prevention of cancer. The claims are directed to methods for

delaying tumor formation and/or slowing tumor progression, which do not require complete elimination of cancer, using a well-defined compound, which methods are fully enabled by the specification.

Section 112, first paragraph, requires that the specification describe the manner and process of making and using an invention so as to enable an ordinarily skilled artisan to make and use the invention as claimed. The instant specification provides such a disclosure of the presently claimed method. For example, the nitroxide or prodrug thereof for use in the invention is described at, e.g., page 7, line 24, through page 10, line 14. Methods of synthesizing the compound are discussed at, for example, page 11, lines 12-26. In addition, the specification teaches how to determine if a particular nitroxide has anti-tumor activity using animal models at, for example, page 6, line 30, through page 7, line 8, and Examples 1 and 2. The specification teaches how to administer the compound and appropriate formulations for specific routes of administration at, for example, page 12, line 8, through page 15, line 12. Appropriate dosages are provided at, for example, page 10, line 26, through page 11, line 11. Furthermore, the application discloses numerous exemplary cancer types that can be treated using the claimed method at, for example, page 6, lines 10-29. In view of the ample disclosure of the application, an ordinarily skilled artisan would know how to make a compound of the pending claims, screen the compound for anti-tumor activity, and use the compound to delay the onset of tumor formation or slow the progression of a tumor *in vivo*. Accordingly, the Section 112, first paragraph, rejection should be removed.

The Office contends that one of ordinary skill in the art could not practice the claimed invention without undue experimentation and cites *In re Buting*, 163 U.S.P.Q. 689 (C.C.P.A. 1969) and a medical textbook in support of its assertions. The Office relies on the 1969 Buting case which has been turned on its head by *In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (C.C.P.A. 1980). Applicants have shown that the compounds of the invention are effective against cancers in animal models, as discussed below. See also *In re Brana*, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Further, there is no question that cancer treatment has advanced in the past 30 years. Enablement inquiry should be dynamic. The Office cited the introduction section of the oncology chapter of medical textbook, which generalizes that different types of cancers have unique biological features (Simone, Oncology. In: Bennett & Plum, eds. *Cecil Textbook of Medicine*, Vol 1. 20<sup>th</sup> ed. Philadelphia, PA: W.B. Saunders Co.; 1996:1004). However, neither the text cited by the

Office nor the office action considers the ability of particular compounds of the inventive method to treat multiple cancers. As evidenced by the Examples of the instant application and references cited below, the compound of the inventive method is effective against a broad range of cancer types.

The Examples provided in the specification demonstrate that the compound of the invention can delay the onset of tumor formation in two different animal models. In Example 1, animals having a p53 deficiency were administered a compound of the claimed method, Tempol. The onset of tumor formation in animals administered Tempol was delayed as compared to control animals that were not administered Tempol. Tempol administration further extended the lifespan of the animals as compared to controls (see specification at page 16). Notably, Tempol delayed the onset of *all* types of tumors that are typically associated with p53 gene defects. Thus, contrary to the assertions of the Office at page 4, the compound of the claimed method has been demonstrated to delay the onset of all cancers associated with p53 deficiencies.

Likewise, Example 2, which is not considered in the Office Action, demonstrates the effectiveness of the inventive method to delay the onset of any type of tumor, including tumors which are not associated with p53 deficiencies. Specifically, Tempol administration to normal C3H mice, i.e., an animal model not modified genetically, dramatically reduced the incidence of *all* types of tumors compared to control mice that were not administered Tempol. Also Mitchell et al., *Free Rad. Biol. Med.*, 34(1), 93-102 (2003) (submitted herewith), reports that Tempol administration to normal C3H mice reduced tumor incidence compared to animals that did not receive Tempol. In addition, Applicants submitted data establishing that Tempol delayed the onset of tumor formation in *Atm*-deficient mice, which is a model of the human cancer prone-syndrome ataxia-telangiectasia by way of the Declaration under 37 C.F.R. § 1.132 of James B. Mitchell submitted March 3, 2000. The manuscript submitted with the declaration has been published by a peer-reviewed journal as Schubert et al., *Hum. Molec. Genet.*, 13(16), 1793-1802 (2004), submitted herewith. Mitchell et al. and Schubert et al. describe Applicants' invention and were published after the filing date of the instant application.

Moreover, the post-filing scientific literature demonstrates that the compound of the invention slows the progression of tumors. For example, Tempol inhibited the growth of three different human breast cancer cell lines, a human ovarian cancer cell line, a human

colon cancer cell line, a hamster ovarian cell line, and a rat liver cancer cell line (Gariboldi et al., *Free Radic. Biol. Med.*, 24(6), 913-923 (1998), submitted herewith). Tempol also exhibited an anti-proliferative effect against the HL60 human promyelocytic leukemia cell line (Monti et al., *J. Cell Biochem.*, 82(2), 271-276 (2001), submitted herewith). In addition, Tempol inhibited the growth of established gliomas tumors *in vivo* (Gariboldi et al., *Eur. J. Cancer*, 39, 829-837 (2003), submitted herewith). The scientific literature clearly demonstrates that administration of Tempol in accordance with the claimed method slows the progression of tumors.

Compounds other than Tempol and encompassed by the pending claims also have anti-tumor activity in the context of the invention. For example, Tempo inhibited the proliferation of prostate carcinoma (Suy et al., *Cancer*, 103(6), 1302-1313 (2005), submitted herewith). In particular, Tempo was administered intratumorally to established prostate carcinoma xenografts, resulting in tumor regression in three of the four tested animals (see Suy et al. at page 1305, paragraph bridging columns 1 and 2, and column 2, paragraph 1; and page 1309, column 2, paragraph 1). Prostate tumor regression also was observed when Tempo was administered intraperitoneally (see Suy et al. at page 1309, column 2, paragraph 1). Tempo was active against both hormone-responsive and hormone-refractory cancer cell lines (see Suy et al. at page 1312, column 1, paragraph 1). In addition, Tempo suppressed tumor growth in human breast tumor-bearing mice (see Suy et al. at page 1309, column 2, paragraph 1).

The authors of the cited references employed the materials and methods disclosed in the specification to predictably delay the onset of tumor formation or slow the progression of tumors. Several types of cancers were demonstrated to be susceptible to treatment using the inventive method; in fact, *all* of the cancer types tested responded to a compound of the claimed method. Therefore, the instant specification provides sufficient guidance so as to enable the ordinarily skilled artisan to make and use the full scope of the invention as claimed without undue experimentation. The rejection of claims 1, 28, 30, and 49 under Section 112, first paragraph, should be withdrawn.

#### *Discussion of Double Patenting Rejection*

Claims 30 and 49 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 22 of the '946 patent and/or

claim 2 of the '619 patent. Claim 30 has been amended, and claim 49 is dependent on claim 30. Applicants respectfully request the withdrawal of the rejection in view of the claim amendments.

*Conclusion*

The application is in good and proper form for allowance. The amendments and remarks place the application in condition for allowance or in better condition for consideration on appeal. The Examiner is respectfully requested to enter the amendments. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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